50. The recombinant influenza virus of claim 39, wherein the tumor antigen is a non-melanoma antigen.

51. The recombinant influenza virus of claim 41, wherein the breast carcinoma antigen is HER-2/neu or MUC-1.

52. The recombinant influenza virus of claim 41, wherein the ovarian carcinoma antigen is HER-2/neu or MUC-1.

53. The recombinant influenza virus of claim 41, wherein the cervical carcinoma antigen is human papilloma virus E6 or E7.

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54. The recombinant influenza virus of claim 41, wherein the ovarian carcinoma antigen is MUC-1.

REMARKS

Applicants have canceled claims 2-5, 20-22, 28 and 29 without prejudice to the Applicants' right to pursue the subject matter of the canceled claims in one or more related applications. New claims 30-54 have been added to more particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. After entry of this amendment, claims 1, 30-54 will be pending in the application; for the Examiner's convenience, a copy of the pending claims is provided as Exhibit A. The new claims 30-54 are fully supported by the instant specification. In particular, support for the claims is provided, *inter alia*, in the specification as described in Table 1 below. Accordingly, no new matter has been added.

CLAIM	SUPPORT IN THE SPECIFICATION
30	• p.3, lines 14-16 • p.8, line 29 to p.9, line 5 • p.9, lines 21-26 • p. 15, line 15 to p.16, line 10
31	• p.9, line 27 to p. 10, line 4 • p. 15, line 15 to p.16, line 10
32 & 33	• p.9, lines 21-2336 & 37
34 & 35	• p.9, lines 23-26
36 & 37	• p.17, lines 12-14 • p. 15, lines 22-26
38	• p. 10, lines 4-9
39, 40 & 41	• p. 8, Table 1
42 & 43	• p.10, line 25 to p. 12, line 31 • p.13, lines 1-4
44	• p.10, line 25 to p. 12, line 31 • p.13, lines 14-16
45-54	• p.8 Table 1

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 1-5 and 20-22, 28, and 29 were pending in the instant application. In the Advisory action, the Examiner maintains his rejections of these claims and refers the Applicant to Paper No. 16, in which the Examiner contends that the specification allegedly does not contain sufficient written description to enable the full scope of the invention as claimed. Although in no way agreeing to the rejections of claims 1-5 and 20-22, 28, and 29, Applicants have canceled claims 2-5 and 20-22, 28, and 29 without prejudice, thus rendering the rejection moot. However, as Applicants discuss below, claim 1 and new claims 30-54 added herein by amendment are enabled by the specification as filed, and the rejection should not be maintained.

Claims 1, and 30-54 are drawn to recombinant influenza viruses comprising a heterologous sequence which encodes a tumor antigen within the influenza viral genome and vaccine formulations thereof. According to the specification, the tumor specific antigen can be inserted into an open reading frame of a genomic segment of the influenza virus genome, preferably into a structural gene of the influenza virus, e.g., HA, NA. Alternatively, the tumor specific antigen may be placed in a bicistronic arrangement with an open reading frame of a genomic segment of the influenza virus genome. The instant specification meets the requirements of the first paragraph of 35 U.S.C § 112 by providing an adequate written description of the invention as claimed.

The instant specification teaches how to construct recombinant influenza viruses using for example, the techniques of reverse genetics, to express tumor specific antigens (*See* the specification at p. 8, line 26 to p . 9, line 5; p. 7, lines 1-16; p. 9 lines to p. 10 line 4; p. 15, line 15 to p. 16, line 10). The specification cites to and incorporates by reference U.S. Patent No. 5,166,057 and International Publication No. WO 93/21306, which provide extensive disclosure to enable one skilled in the art to engineer recombinant influenza viruses containing tumor antigens. Through the working example presented, the instant specification provides a detailed experimental procedure on how to engineer a recombinant influenza virus expressing a model tumor antigen, β-gal (*See* the specification at p. 15, line 15 to p. 22, line 12).

β-gal was used as an illustrative example for the methods and recombinant influenza viruses of the invention. The Example provided in the instant specification (*See* the specification at p.15 line 15 to p. 26, line 24) describes the construction, characterization, and *in vivo* efficacy of a recombinant influenza vector expressing β-gal, a model tumor antigen, in the context of cancer immunotherapy. The recombinant influenza virus carrying β-gal was effective at reducing tumor metastases in an animal model (*See* the specification at p. 19, line 10 to p. 22 line 12). Mice immunized with the recombinant influenza virus were able to generate high levels of cytotoxic T-cell response against the expressed antigen (*See* the specification at p.20 line 25 to p.21 line 28). Treatment with the recombinant influenza virus mediated regression of an experimental murine cancer model (*See* the specification at p.22, lines 1-15).

At the time of filing of the instant application, β-gal was used by those skilled in the art as the prototypic tumor model system in experimental studies (*See* Chen et al., 1996 J. Immunol. 156:224-231; reference AH on the record; ("Chen"); Wang et al., 1995 J. Immunol. 154:4685-92; reference BD on the record ("Wang"); and Rao et al., 1996 J. Immunol. 156: 3357-65; reference AY on the record; ("Rao")). According to Wang, β-gal was characterized in the art as a "model tumor marker". Rao also hypothesizes that β-gal is most appropriate as a model for tumor antigens resulting from, for example, viruses or genetic events that result in expression of foreign proteins arising from mutations. In fact, many of the tumor antigens cited in the instant specification are derived from the expression of foreign proteins arising from mutations or from viruses. Therefore, in view of the foregoing, β-gal is a recognized model for the study of tumor antigens and thus, an ideal prototypic system for establishing the claimed invention. One skilled in the art would be able to apply the teachings of the instant application, using β-gal as a model system to other tumor antigens.

Structures of the tumor antigens (*e.g.*, the polynucleotide sequences of the tumor antigens) that can be used in accordance with the invention were known in the art as of the filing date of the instant application. Many relevant publications regarding tumor antigens are cited in the specification (*See* the specification at p. 2 lines 16-35; Robbins et al, 1996, Curr. Opin. Immuno. 8:638-636; ("Robbins")), and examples of specific tumor antigens are provided in the instant specification (*See* the specification at p. 8, Table 1).

Molecular and structural characterization of the specific tumor antigens cited in the specification were well known in the art at the time of filing of the instant application. A review of the art at the time of filing of the instant application indicates that the art indeed provided ample guidance to one skilled in the art regarding identification of tumor antigens, for example, either through gene transfection methodologies or biochemical methods (*See* Van Pel et al., 1995 Immunol. Rev. 145: 229-250; ("Van Pel"); *See* also Robbins). Moreover, the art provided methods for identification of the actual peptide sequence, derived from the tumor antigens, required to be recognized by cytotoxic T lymphocytes and subsequently elicit a cellular immune response (*See* Van Pel, Robbins). The art also provided methods for the isolation and identification of novel tumor antigens.

The Examiner's attention is invited to the following references of record: Itoh et al., 1997 Int. Rev. Immunol. 14(2-3):153-171 ("Itoh"); Kawakami et al., Keio J. Med., 1996,

45(2): 100-8 ("Kawakami-1"); Kawakami et al., Immunol. Res., 15: 179-190 ("Kawakami-2"); references BG, BH, and BI, respectively. As demonstrated in these publications, human melanoma antigens, including melanocyte specific proteins (*e.g.*, MART-1, gp100, tyrosinase, and TRP-1), tumor-specific antigens (*e.g.*, MAGE-1, MAGE-3, BAGE, and GAGE), and tumor specific mutated antigens (*e.g.*, β-caternin, MUM-1, CDK4), had all been identified either through genetic or biochemical techniques as of 1996, well before the filing of the instant application. Additionally, the sequence of the epitopes derived from these tumor antigens that would be recognized by T lymphocytes had also been identified as of the filing date of the instant application. In fact, Robbins provides a detailed review of all the tumor antigens that had been identified as of 1996, prior to the filing of the instant application. The Examiner's attention is respectfully invited to Robbins, Table 1, p. 629, where Robbins presents melanoma and non-melanoma antigens, and the corresponding publications that identified them, as well as the specific epitopes derived from them that are recognized by cytotoxic T lymphocytes. The tumor antigens disclosed in Robbins, correspond to those disclosed in the instant specification at p.8 Table 1. Therefore, the nucleotide sequences of the tumor antigens that can be used in accordance with the invention were known in the art as of the filing of the instant application (For a further detailed review of the nucleotide sequences of the tumor antigens for use in the methods of the invention the Examiner's attention is invited to the Amendment filed by the Applicants on March 13, 2002).

Methods for determining the structural motifs and molecular determinants required for recognition of tumor antigens by T lymphocytes had been established, prior to the filing of the instant application, as reviewed by Van Pel and Robbins. For example, Van Pel describes a nonameric peptide derived from MAGE-1, where each residue of the peptide was mutated and tested in turn for its ability to bind T lymphocytes. The experiments presented indicated that amino acids at positions 3 and 9 were critical for anchoring the peptide to the MHC class I groove of the T-cell.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). In fact, the

specification need not describe and should preferably omit well known subject matter in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1367, 231 UPSQ 81 (Fed. Cir. 1986); *In re Hayes Microcomputer Products, Inc. Patent Litigation*, 982 F. 2d. 1527, 25 USPQ2d 1241 (Fed. Cir. 1992); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990). These enablement rules preclude the need for the patent application to "set forth every minute detail regarding the invention" or to "disclose that which is already well known in the art" since the patent application speaks to those skilled in the art. *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991).

In view of the foregoing, Applicants assert that the specification fully describes the claimed invention, and coupled with the state of the art at the time the application was first filed, one skilled in the art can make and use the claimed invention without having to resort to undue experimentation. Any of the tumor antigens presented in the specification can be readily engineered by a skilled artisan into a recombinant influenza virus using the methods provided in the specification. The invention as claimed is fully enabled and when combined with the state of the art at the time of filing would allow the skilled artisan to practice the claimed invention. For example, given that the determination of the peptide sequences of tumor antigens was routine in the art, the skilled artisan can readily deduce the nucleotide sequence from the peptide sequence and combined with, for example, the reverse genetics technique disclosed in the instant specification engineer recombinant influenza viruses carrying the appropriate nucleotide sequences, encoding the tumor antigens or fragments thereof.

The art provides ample guidance regarding identification of tumor antigens and their epitopes which can be used by one skilled in the art to engineer the recombinant influenza viruses of the invention. Any tumor antigen well-known in the art can be readily substituted for the prototype antigen, β-gal, described in the example in the specification. A skilled artisan armed with the knowledge of the nucleotide sequences of tumor antigens as of the filing date of the application can easily substitute any tumor antigen, in place of the tumor antigen used in the example, and obtain a recombinant influenza virus containing a desired

tumor antigen. Thus, one of skill in the art, as of the filing date of the instant application, would have known how to make and use a recombinant influenza virus having a genome comprising a heterologous sequence encoding a tumor antigen.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. The claims are believed to be free of the art and patentable. Withdrawal of all the rejections and objections and an early allowance are earnestly sought.

If any issues remain, the Examiner is requested to telephone the undersigned.

Respectfully submitted,

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